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26

(19) World Intellectual Property Organization
International Bureau





(43) International Publication Date 26 September 2002 (26.09.2002)

PCT

(10) International Publication Number WO 02/074327 A3

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- (21) International Application Number: PCT/US02/07379
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- (25) Filing Language:

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(26) Publication Language:

English

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- (72) Inventor; and
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- (74) Agents: DONOVAN, Stephen et al.; c/o Allergan Sales, Inc., 2525 Dupont Drive, Irvine, CA 92612 (US).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

074327

(54) Title: COMPOSITIONS AND METHODS FOR TREATING GONADOTROPHIN RELATED ILLNESSES

(57) Abstract: The present invention relates to an agent comprising a neurotoxin, methods for making the agents and methods for treating endocrine disorders, for example gonadotrophin related illnesses. Preferably, the agent comprises at least a portion of a botulinum toxin.

INTERNATIONAL SEARCH REPORT

International application No.

PCT.	/USO2	/07379

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : A61K 38/16, 38/22, 38/24, 38/48; C12N 9/52 US CL : 424/94.63, 530/399, 435/220, 514/2, 12 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S.: 424/94.63, 530/399, 435/220, 514/2, 12 Documentation searched other than minimum documentation to the extent that such documents are included in the fields search commentation searched other than minimum documentation to the extent that such documents are included in the fields search Please See Continuation Sheet C. DOCUMENTS CONSIDERED TO BE RELEVANT Category * Citation of document, with indication, where appropriate, of the relevant passages Relevant to classification and IPC X US 5,707,964 A (NETT et al.) 13 January 1998 (13.01.98), entire document. 1-25 X WO 90/09799 A1 (COLORADO STATE UNIVERSITY RESEARCH FOUNDATION) 07 1-2, 9, 11-)		
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September 1990 (07.09.1990), entire document	24		
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Y US 5,939,070 A (JOHNSON et al.) 17 August 1999 (17.08.1999), entire document 3-8, 10, 2	5		
Y US 5,989,545 A (FOSTER et al.) 23 November 1999 (23.11.1999), entire document. 3-8, 10, 2			
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Special categories of cited documents: "I" later document published after the international filing date or priority			
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"X" document of particular relevance; the claimed invention cannot earlier application or patent published on or after the international filing date considered novel or cannot be considered to invention canno	at be		
and an about the state of the s			
"L" document which may throw doubts on priority claim(s) or which is rive to	acceptable when they move move the priority claim(s) or which is cited to		
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establish the publication date of another citation or other special reason (as specified) document of particular relevance; the claimed invention cannot considered to involve an inventive step when the document is combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents.			
establish the publication date of another citation or other special reason (as specified) document of particular relevance; the claimed invention cannot considered to involve an inventive step when the document is combined with one or more other such document is combined with one or more other such documents.			
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establish the publication date of another citation or other special reason (as specified) O" document referring to an oral disclosure, use, exhibition or other means O" document published prior to the international filing date but later than the priority date claimed Oate of the actual completion of the international search O which is cited to serve the claimed invention cannot considered to involve an inventive step when the document is combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents, such combined with one or more other such documents or more other such documents with one or more other such documents with one or more other such documents or more other such documents or more other such documents. One of the actual completion of the international search One of the actual completion of the international search One of the actual completion of the international search			
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INTERNATIONAL SEARCH REPORT	PCT/US02/07379
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Dialog files 155, ,5 35, 349 (MEDLINE, Biosis, Dissertation Abs., PCT full text); gonadtrophin, releas?, hormone, receptor, bind? affinity, target?, toxin, neurotoxin	WEST files USPT, DWPI search terms: GNRH, n?,
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